Draft ASHP Guidelines on Appropriate Off-Label Medication Use

Purpose

The American Society of Health-System Pharmacists (ASHP) believes that prescribing, dispensing, and administration of drug products for off-label medication use often represents a therapeutic approach that has been extensively studied and is supported by the medical literature. Drug therapy decisions of healthcare professionals and patients should not be limited by third-party reimbursement standards that are based solely on FDA-approved drug products and their subsequent labeling. Instead, some degree of flexibility must be maintained in order optimize patient outcomes and allow for individualized care. While the ultimate responsibility for the safety and efficacy of off-label use resides with the prescriber, the hospital or health-system's pharmacy and therapeutics (P&T) committee, policy and procedures, and pharmacists should all take part in managing and supporting off-label medication use. The ultimate goal is to improve patient access to the most appropriate, efficacious treatment for each patient and their disease.

Off-label usage applies to any use of a medication in a manner including the diagnosis, combination with other medications, dosage, frequency, route of administration, line of therapy, or age of the patient that is not specifically approved by the FDA and delineated on the label given to the drug during the approval process.[1] It is common for the drug products' labeling to fail to represent the most current therapeutic information.[2] This can be attributed to several factors. 1) Any changes to the approved FDA label for a medication must be submitted to the FDA by the manufacturer and this can be a time consuming and expensive process. 2)

The body of medical knowledge is constantly expanding including publications demonstrating the value of medications in settings other than the original FDA approved labeling. 3) Legally, prescribers are not limited to FDA labeled indications when making the best therapeutic decision for their patients. Therefore, in many clinical situations, off-label use represents the most appropriate therapy for patients. Failure to recognize these circumstances or, more importantly, regarding such uses as unapproved or experimental, may restrict patient access to necessary drug therapies. However, distinction must be made between evidence-based off-label use and the inappropriate use of off-label drugs. By definition, evidence-based off-label use demands the support of clinical trials and case reports. In contrast, inappropriate off-label use has little or no literature support. Inappropriate use of off-label drugs must be avoided due to efficacy and safety concerns resulting from the drug bypassing any risk-benefit analysis.[3] In addition to the limitations of FDA approved indications, there are also limitations to guidelines and standards of practice recommendations produced by professional organizations. This is due primarily to the constant influx of new literature resulting in the continual evolution of standards of practice, making it difficult for professional societies to review scientific data expediently and develop standards that remain absolutely current.

Impact of Off Label Medication Use

When discussing off-label medication use, the site of care must be considered due to variation in prevalence and urgency. For example, inpatient situations related to the treatment of life-threatening conditions or end-organ damage will require more immediate action than more general inpatient or outpatient situations. For infused medications, certain settings and

particular populations demand more prevalent use of off-label treatment regimens. These include oncology, rare diseases and pediatric practices which have a tendency to exhibit patterns of off-label drug usage.[4,5] Targeted therapies have increased off label usage in oncology due to the supporting science and clinical benefits demonstrated for the same target in multiple cancer types. Furthermore, oral medications and injectable medications for self-administration by the patient in a home setting often lack direct oversight by a clinical pharmacist, relying on payer scrutiny and off-label justification by the dispensing pharmacist. In contrast, infusion and specialty medications given in the hospital setting demand pharmacist oversight and further involvement in the off-label process. Differences by payer limit the utilization of off-label medications in all settings, basing their coverage decisions on levels of criteria including approved compendia listings, payer specific clinical policies, or submission of peer-reviewed evidence based literature. It is important to consider that payer policies do not always reflect what is medically necessary for the individual patient, indicating the need for a structured off-label medication use process within each institution.

Recommendations

Use of P&T Guidelines. The P&T committee should be considered the arbiter of institutional policies regarding off-label medication use and should rely on scientific evidence to guide its decisions.[6] When considering off-label use, supporting safety and efficacy evidence must be carefully evaluated and a risk–benefit determination made, especially when alternatives with FDA-approved labeling are available. The P&T committee should implement a systematic approach to evaluating evidence and benefits before approval of off-label drug therapy.

Furthermore, when the off-label use of a drug product is expected to occur frequently, the P&T committee should consider establishing protocols guiding that use in order to expedite the process, especially when the potential benefits and harms are difficult and time-consuming to quantify.

Use of Formulary Restrictions. Formulary management should include selection of medications that optimize patient care and outcomes while also curbing unnecessary off-label usage. In the inpatient setting, restrictions for non-formulary medications and approval requirements before administration protect the institution from financial loss due the lack of a separate structure for reimbursement of medications (except in rare situations where carve outs exist). In the outpatient setting, the implementation of a restrictive formulary and increased payer scrutiny should further limit unnecessary off-label usage. In either case, both inpatient or outpatient use of medication that falls outside of the approved formulary or lacks the appropriate evidence based support, should undergo a formal review process including a peer review of medical necessity and evaluation of patient safety. Consideration should be given to restricting all outpatient infused specialty and high dollar medications to their FDA approved indications when added to the formulary. Doing so ensures that an off-label process is initiated with every use that falls outside of the FDA approved indication.

Defined Off-Label Policy and Practice. With the introduction of newer, expensive specialty agents that are being prescribed in various disease states, the propensity to use medication outside the label poses a significant financial risk in addition to the patient care risks outlined

above. The implementation of an off-label protocol mitigates the risk of payment denial, informs patients of their payment responsibility and helps to ensure fiscal viability of the practice. Development of specific criteria is necessary and should take into consideration the medication, duration, utilization and monitoring of the treatment. The rationale for usage should be documented and supported and the patient should be educated and consented if warranted. It is pertinent that the prescriber who is considering the use of a medication for an off-label indication have a face-to-face discussion of the off-label clinical and financial benefits and risks with the patient, document that conversation within the medical record, and have the patient sign an Advanced Beneficiary Notice (ABN) or Notice of Non Coverage (NONC) as applicable.

The cost of a medication is a significant consideration whether it will be administered in the outpatient or inpatient setting; however, the outpatient reimbursement structure for most payers provides for expensive medications to be separately reimbursed (unlike the inpatient setting, where a set payment or DRG is all that will be reimbursed, despite the costs of the individual medications administered). For commercial and Medicare Advantage patients in the outpatient setting a pre-determination should be conducted to gain approval for off-label use prior to the patient receiving the medication. This is also true for commercial or Medicare Advantage patients in the inpatient setting who will need continuation of their therapy in the outpatient setting. For payers who do not provide a process for pre-determination (traditional Medicare and Medicaid), guidance from CMS National and Local Coverage Determinations (NCD/LCD), CMS approved drug compendia, or CMS peer reviewed literature should be referenced to ensure the necessary level of support. In some cases, commercial payers publish

their own clinical guidelines and policies which should be referenced as well, but most follow or closely align to the requirements outlined by CMS. In both situations, access to the off-label treatment should be dependent upon NCD/LCD support, the presence of the indication on one of the CMS approved compendia, or sufficient peer review evidence (two Phase II or one Phase III study). Detailed algorithms that outline an example off-label medication policy differentiated by payer can be found in Appendix B.

Use of Internal Peer Review. A more rigorous process for approval should be implemented in the case of innovative off-label medication use, in which the prescriber's requested treatment is based upon reasonable rationale but lacking sufficient supporting evidence related to safety, efficacy, and cost-effectiveness.[7] In these cases, an escalation process should exist within the institution or practice that provides for existing literature, case reports and pertinent clinical patient information to be submitted for peer review to a disease-specific leader or a division director. If the reviewer(s) determines that there is insufficient evidence to support the requested use, the use of the medication is not recommended and other alternatives should be considered.[8]

Reconsideration Request. Medicare claims for off-label use are more likely to be denied, when compared to commercial payers, due to the lack of an existing pre-determination process. However, CMS allows for a formal process for requesting revisions to current policy and guidelines unrelated to any single patient treatment if deviations from the evidence or standard of practice are identified with Medicare.[9] Submitted requests should demonstrate safety and

benefit to a patient population through inclusion of peer-reviewed literature (phase II or III trials and patient cases may be considered) and thorough explanation of how the current coverage deviates from the literature. When applicable, examples of other payer policies such as a commercial payer or an LCD in a different region that include the requested coverage should be referenced as additional support. Formal requests can be submitted for both NCD and LCD, however the NCD reconsideration process is more rigorous and time-consuming as they often require open comment periods. Requests for changes in commercial payer policies and clinical guidelines should follow an identical approach.

Pharmacists at the Point of Care. ASHP believes that health-system pharmacists bear responsibility for ensuring optimal patient outcomes from all drug therapy and therefore should play a significant role in respect to off-label use. When embedded in the patient care team, pharmacists can assist in determining the appropriateness of the medication use and providing the supportive information when medications are prescribed outside of the defined scope of the FDA label. Pharmacists, in collaboration with the patient care team, can provide the financial team with all the information necessary to begin the pre-determination process.

Use of Manufacturer/Reimbursement Support Services. When specialty, high cost, infused and injectable medications are prescribed for an off-label indication, it is essential to know a patient's pharmacy and medical insurance coverage and the availability of assistance programs for the prescribed medication. Because benefits will vary based on site of care, distinction should be made between the pharmacy benefit plan and medical benefits when determining

coverage. Reimbursement support services provided by many manufacturers help the patient to understand their out of pocket cost share and provide information on the availability of manufacturer copay assistance or foundation copay assistance support. In the event that the off label use results in an insurance denial, some pharmaceutical manufacturers also offer assistance with the appeal process. In addition, some pharmaceutical companies may provide the patient with free medication if the patient meets both the clinical and financial requirements to qualify for their program. It is recommended to have dedicated pharmacy staff available to assist patients in navigating and accessing these resources. Since some companies will ship replacement or free drug directly to the institution for patients who qualify, it is also important to ensure these drugs will be received directly by pharmacy personnel. Lastly, it is important to note that not all pharmaceutical companies will provide assistance outside of the FDA approved usage, so reliance solely on these programs to provide support is not recommended.

Request for External Peer Review. Most commercial payers provide for the opportunity of a peer to peer discussion between the attending physician and a peer physician employed by the payer (or hired as a consultant) when a predetermination request for an off label use of a medication has been denied. It affords an opportunity for the attending physician to speak with a medical director or physician reviewer about the denial. By requesting this conversation, the attending physician can share critical clinical information or rationale that may not have been adequately conveyed by the pre-determination and emphasize the opportunity for an outcome that is supported by the published data. Peer to peer discussions are most effective when the

physician reviewer is an expert in the specialty for which the indication is intended to be used. Organizations requesting to schedule a peer to peer discussion should be specific and request a physician specialist familiar with the disease for which the medication is intended to treat.

Pharmacists as Reimbursement Experts. In addition to their value at the point of care in supporting the safe and effective use of off-label medications, it is also important to employ pharmacists who understand all aspects of medication reimbursement and the revenue cycle. This includes knowledge of payer policies and payer approval processes, use of medication assistance programs, understanding of clinical guidelines, reconsideration packet preparation, an understanding of the appeals process for drug denials, etc. Most important to these roles is the ability to bridge the clinical and financial worlds, a critical skill to ensure appropriate reimbursement for off-label medication use. These experts stay current with the changing healthcare landscape of both governmental and commercial plans to ensure financial success when infused and specialty medications are administered. They attend Payer Relations meetings, gathering important information regarding upcoming changes and addressing specific payment concerns encountered with specific patients or groups of patients. They are critically important for their ability to translate timely payer and policy requirements to the administrative and front line pharmacy staff to ensure receipt of appropriate reimbursement for the services provided.

Conclusion

With the rate at which scientific evidence is evolving, specialty areas such as oncology,

neurology, dermatology and others will continue to be challenged with off-label medication use. The "personalization" of therapies will further contribute to the growth of off-label use as biomarkers are identified in patients with a disease not covered by the initial FDA approved indication. ASHP acknowledges that off-label medication use often represents the best choice of therapy for a patient and their disease. By implementing an off-label medication use policy that incorporates our best practice guidelines, institutions will improve patient access to the most efficacious treatment options, ensure patient safety and reduce financial risk to the patient and the institution.

Appendix A

Advanced Beneficiary Notice (ABN): a written notice which a physician or designee must provide a patient with Original Medicare that informs the patient that Medicare may not pay for the medication and that the patient may be responsible for payment if the claim is denied. An ABN should be issued prior to the patient receiving an item or service.[10]

Appeal: the process used when a party (for example, a beneficiary, provider, or supplier) disagrees with an initial determination or a revised determination for health care items or services. For example, an appeal can be initiated after denial of a claim, in which insurance company or carrier refuses to honor the request of a payer or individual to pay for healthcare services provided by a healthcare provider.

CMS Approved Compendia: a reference that serves as a comprehensive listing of FDA-approved drugs and biologicals and is recognized as an authoritative source when determining

medically-accepted indications for off-label use. The five compendia listed as well as the requirements to be identified as medically accepted evidence by Medicare are listed as:

Elsevier Gold Standard Clinical Pharmacology: if narrative text is supportive

American Hospital Formulary Service (AHFS) Drug Information: if narrative text is supportive

Truven Health Analytics Micromedex DrugDex: if indication is Class I, IIa, IIb

National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium: if indication is Category 1 or 2a

Wolters Kluwer Lexi-Drugs®: Level A [11]

Reconsideration Packet: a method by which interested parties can request a complete or partial revision to an active LCD. The reconsideration process is available for final LCDs only to the fiscal intermediary (FI). Requests must identify the language that the requestor wants added or deleted as well as include justification for the change supported by new evidence in the medical literature. Legible hard copies of published evidence must be included.

National and Local Coverage Determinations (NCD or LCD): A determination whether or not an item or service is reasonable or necessary for a Medicare beneficiary. A NCD guidance document provides broad guidelines for all Medicare beneficiaries, whereas the LCD is a decision made by the fiscal intermediary or carrier under part A or part B for the location of the patient is treated.

Notice of Non Coverage (NONC): a written notice given to a patient who is covered under a commercial insurance plan before the patient receives a medication for an off-label indication that has been denied for payment (e.g. unsuccessful predetermination), in which the patient may be responsible for payment.

Payer requirements: guidelines for reimbursement decisions vary between payers.

i. ***Commercial:*** use clinical guidelines, pathways and policies; some defer to CMS requirements (NCD, LCD, approved compendia, evidence from approved peer reviewed journals)

ii. ***Medicare vs Medicare Advantage:*** original Medicare is governed by Local and National Coverage Decisions (LCD and NCD), CMS approved compendia, and evidence form CMS peer reviewed journals. For Managed Medicare refer to Commercial above.

iii. ***Medicaid vs Managed Medicaid:*** Medicaid is similar to original Medicare. Refer to Commercial above for Managed Medicaid

iv. ***VA:*** Restricted formulary and clinical guidelines

Peer-to-Peer Discussion: a medical peer-to-peer review process occurs when an institution or practice requests for a specific patient case to be reexamined following an adverse clinical determination being made for that patient. This process allows the attending, treating or ordering physician to provide additional information regarding the patient situation and further discuss the case with the intent to override the initial adverse determination.

Peer Reviewed Scientific Journal: a journal that has submitted most of its published articles for review by experts who are not part of the editorial staff. The numbers and kinds of manuscripts sent for review, the number of reviewers, the reviewing procedures and the use made of the reviewers' opinions may vary, and therefore each journal publicly discloses its policies in the Instructions to Authors for the benefit of readers and potential authors.[10]

Publications recognized by the Center for Medicare and Medicaid Services:

American Journal of Medicine;

Annals of Internal Medicine;

Annals of Oncology;

Annals of Surgical Oncology;

Biology of Blood and Marrow Transplantation;

Blood;

Bone Marrow Transplantation;

British Journal of Cancer;

British Journal of Hematology;

British Medical Journal;

Cancer;

Clinical Cancer Research;

Drugs;

European Journal of Cancer (formerly the European Journal of Cancer and Clinical Oncology);

Gynecologic Oncology;

International Journal of Radiation, Oncology, Biology, and Physics;

The Journal of the American Medical Association;

Journal of Clinical Oncology;

Journal of the National Cancer Institute;

Journal of the National Comprehensive Cancer Network (NCCN);

Journal of Urology;

Lancet;

Lancet Oncology;

Leukemia;

The New England Journal of Medicine; or

Radiation Oncology

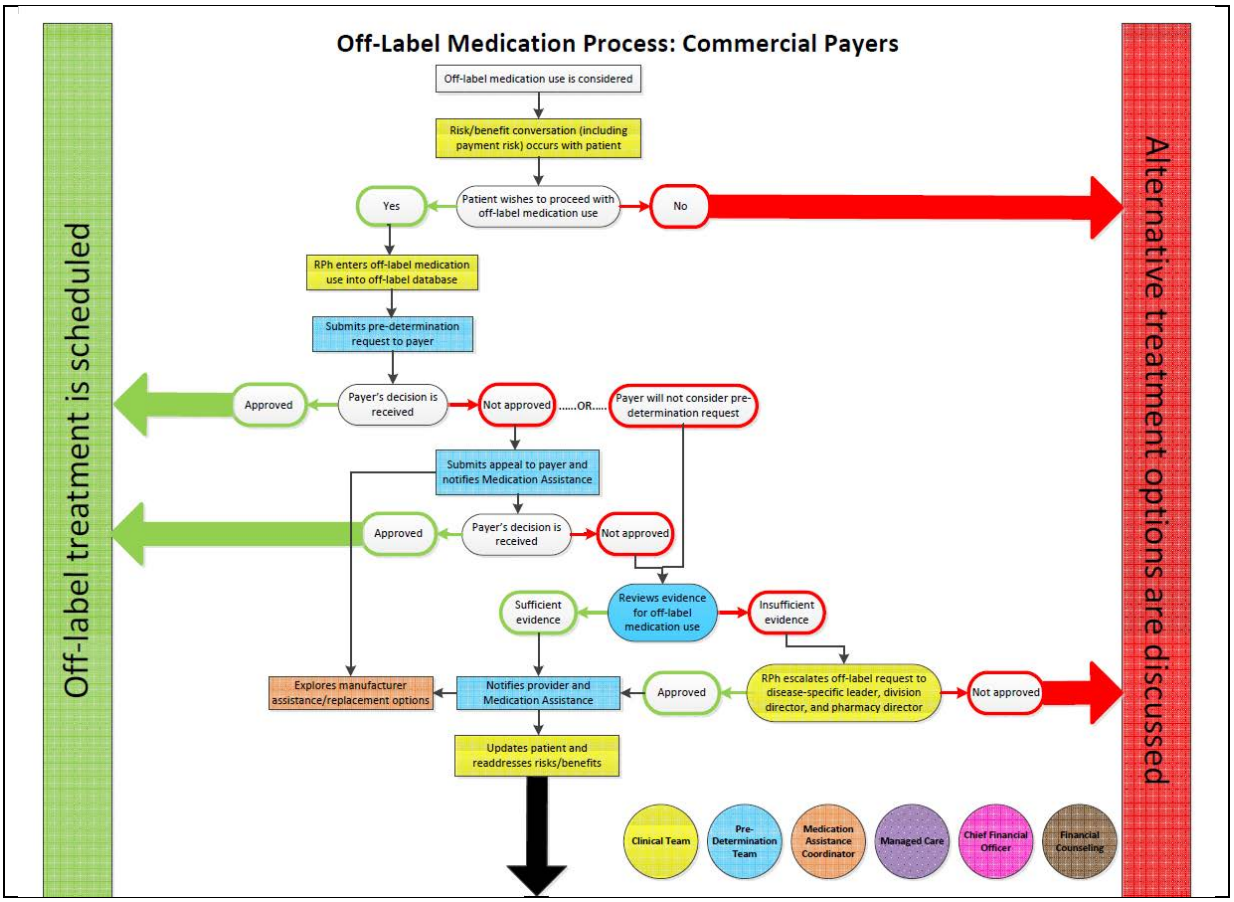
Pharmacy benefit plan: the level of health insurance coverage, which pays for prescription drugs or medications. This can be provided through retail, specialty or mail order pharmacies. In contrast to the medical benefit, this is the benefit typically pays for procedures, physician visits, medication infusions and injection conducted in a physicians' office or infusion center.

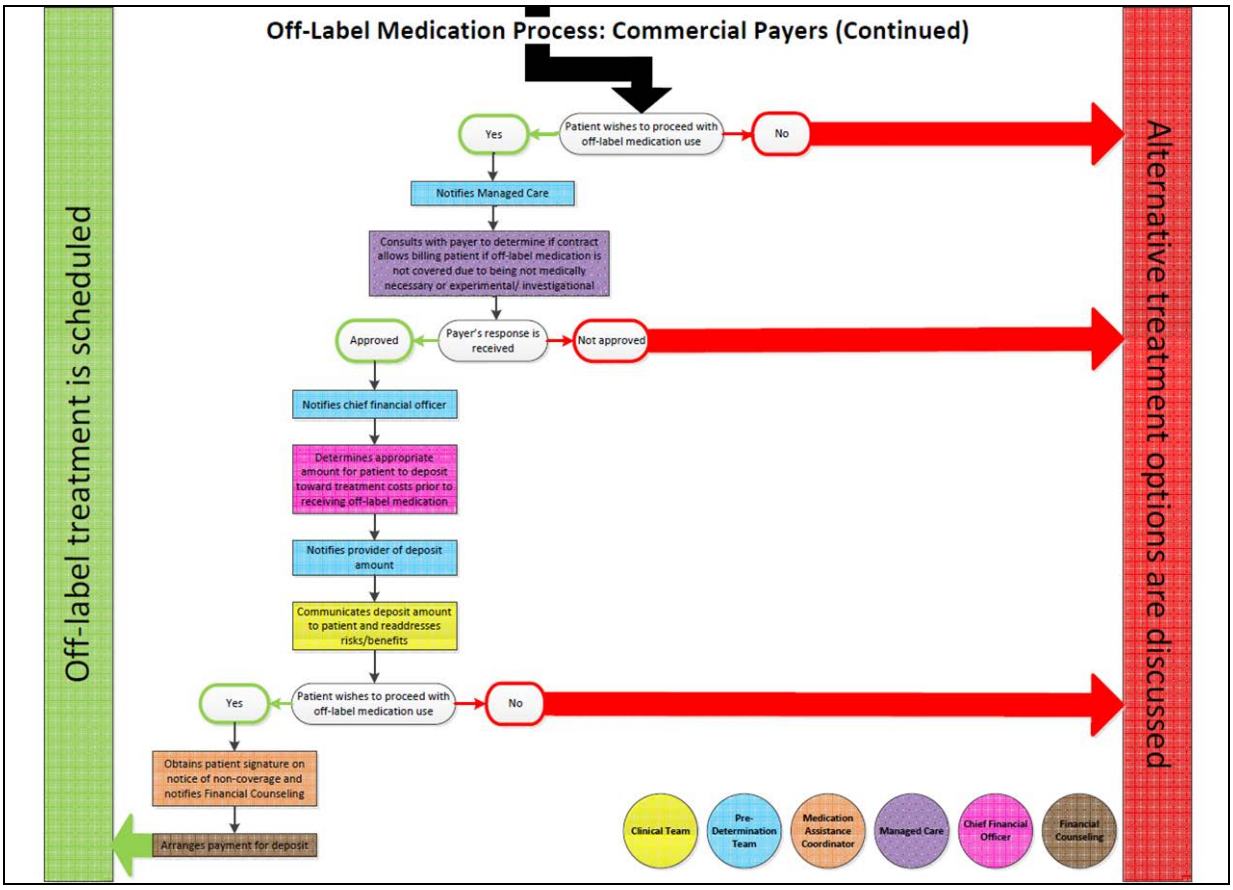
Pre-determination: A process whereby a submission to an insurance company initiates a patient specific review of clinical information when a medication use is deemed off-label to determine if it is to be considered medically necessary, not medically necessary, experimental or investigational and not medically necessary. The insurance company reviews standard medical practice, relevant peer reviewed scientific published data, physician and professional society recommendations and other relevant clinical factors as they relate to the patient's clinical circumstances.

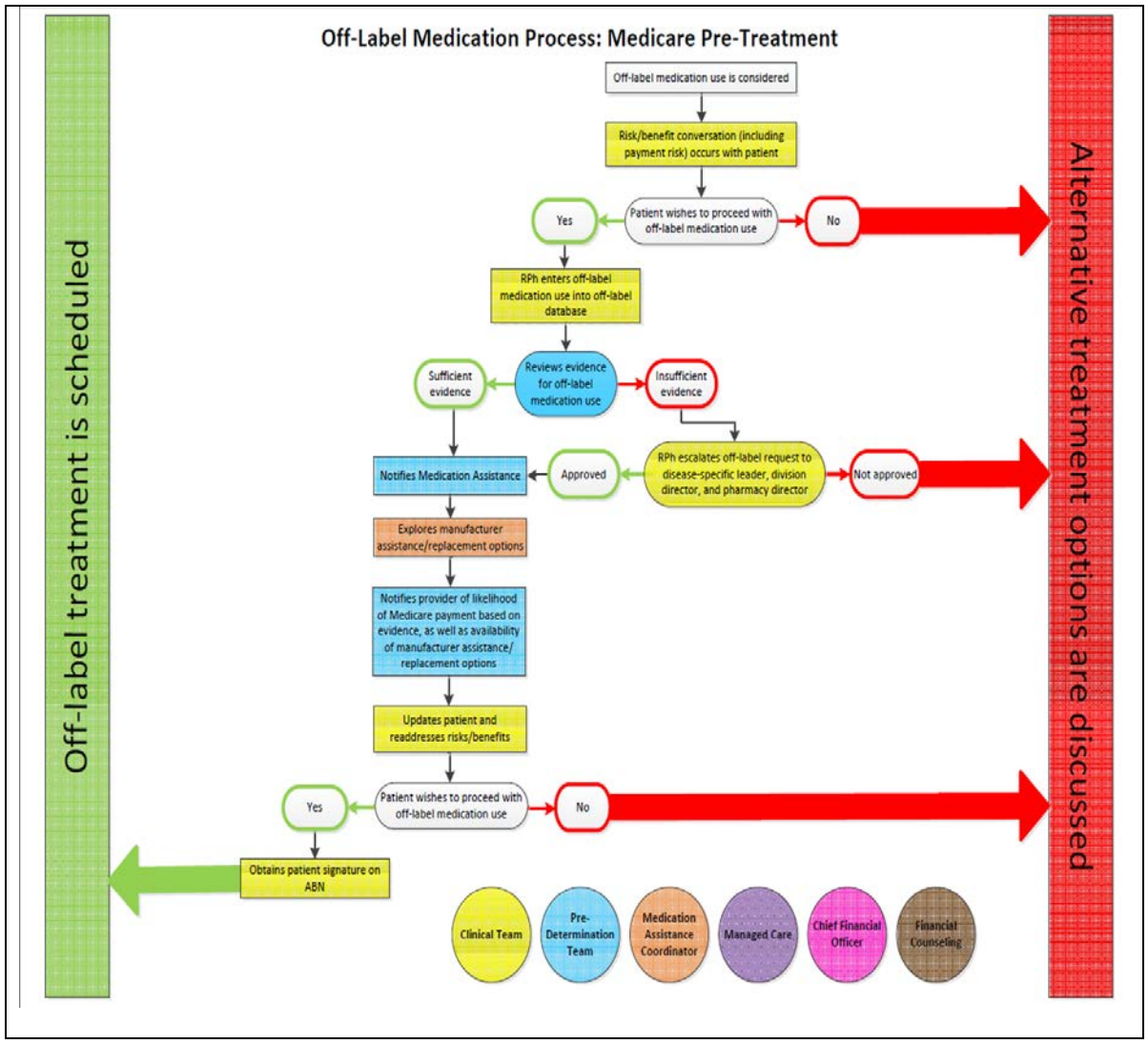
Prior Authorization/Pre-Certification: a requirement of the insurance company which includes evaluation of the medical necessity, appropriateness and efficient use of health care services, procedures and facilities under the provisions of the patient's health benefits plan.[12]

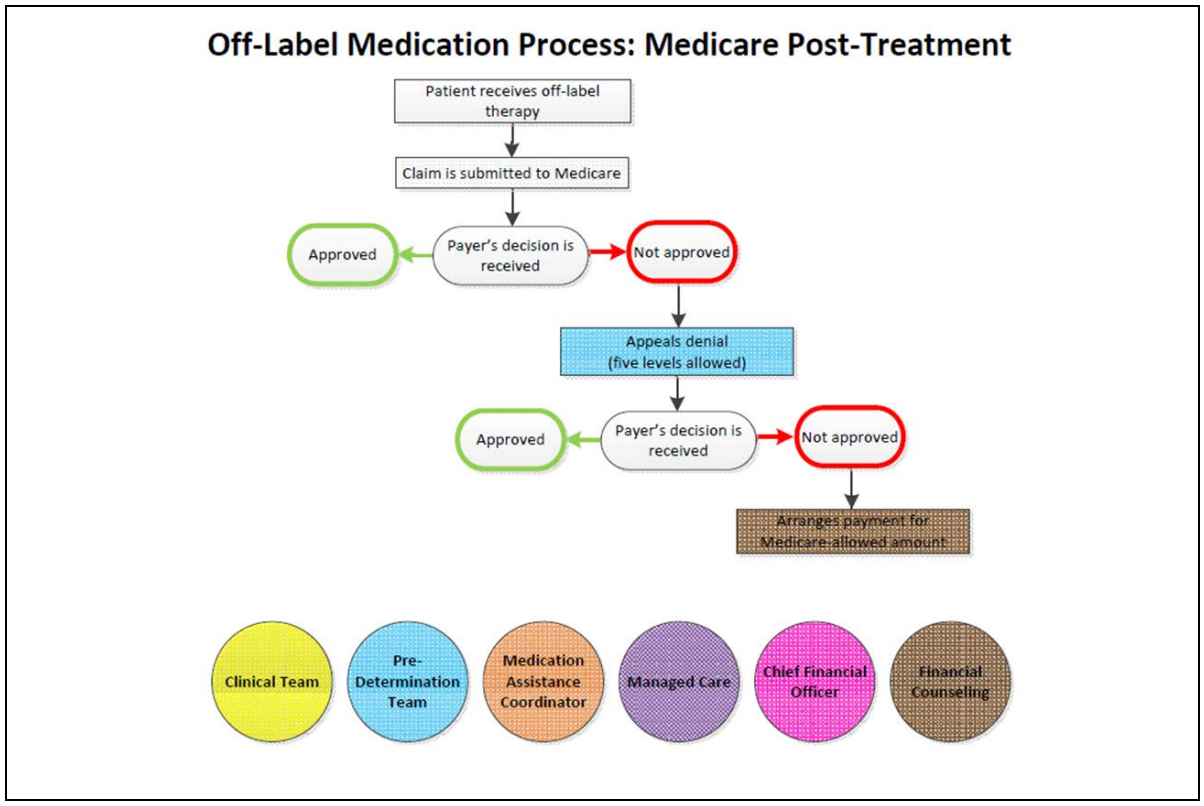
Published Guidelines (ASCO, NCCN, Chest, etc.): systematically developed statements to assist practitioners and patient decisions about appropriate health care for specific circumstances which may include reviews of research about the potential benefits and harms of alternative drugs, devices, and other healthcare services in order to provide the best evidence to inform clinical decisions. Trustworthy guidelines should be based on a systematic evidence review, developed by panel of multidisciplinary experts, provide a clear explanation of the logical relationships between alternative care options and health outcomes, and provide ratings of both the quality of evidence and the strength of the recommendations.[13]

Appendix B


Off-Label Medication Process: Commercial Payers
Off-label medication use is considered
Risk/benefit conversation (including payment risk) occurs with patient
Patient wishes to proceed with off-label medication use
Yes
No
RPh enters off-label medication use into off-label database
Submits pre-determination request to payer
Payer's decision is received
Approved
Not approved
.....OR.....
Payer will not consider pre-determination request
Submits appeal to payer and notifies Medication Assistance
Payer's decision is received
Approved
Not approved
Reviews evidence for off-label medication use
Sufficient evidence
Insufficient evidence
RPh escalates off-label request to disease-specific leader, division director, and pharmacy director
Approved
Not approved
Notifies provider and Medication Assistance
Explores manufacturer assistance/replacement options
Updates patient and readdresses risks/benefits
Clinical Team
Pre-Determination Team
Medication Assistance Coordinator
Managed Care
Chief Financial Officer
Financial Counseling
Off-label treatment is scheduled
Alternative treatment options are discussed


Off-Label Medication Process: Commercial Payers (Continued)
Off-label treatment is scheduled
Alternative treatment options are discussed
Patient wishes to proceed with off-label medication use
Yes
No
Notifies Managed Care
Consults with payer to determine if contract allows billing patient if off-label medication is not covered due to being not medically necessary or experimental/ investigational
Payer's response is received
Approved
Not approved
Notifies chief financial officer
Determines appropriate amount for patient to deposit toward treatment costs prior to receiving off-label medication
Notifies provider of deposit amount
Communicates deposit amount to patient and readdresses risks/benefits
Patient wishes to proceed with off-label medication use
Yes
No
Obtains patient signature on notice of non-coverage and notifies Financial Counseling
Arranges payment for deposit
Clinical Team
Pre-Determination Team
Medication Assistance Coordinator
Managed Care
Chief Financial Officer
Financial Counseling


Off-Label Medication Process: Medicare Pre-Treatment
Off-label medication use is considered
Risk/benefit conversation (including payment risk) occurs with patient
Patient wishes to proceed with off-label medication use
Yes
No
RPh enters off-label medication use into off-label database
Reviews evidence for off-label medication use
Sufficient evidence
Insufficient evidence
RPh escalates off-label request to disease-specific leader, division director, and pharmacy director
Approved
Not approved
Notifies Medication Assistance
Explores manufacturer assistance/replacement options
Notifies provider of likelihood of Medicare payment based on evidence, as well as availability of manufacturer assistance/ replacement options
Updates patient and readdresses risks/benefits
Patient wishes to proceed with off-label medication use
Yes
No
Obtains patient signature on ABN
Off-label treatment is scheduled
Alternative treatment options are discussed
Clinical Team
Pre-Determination Team
Medication Assistance Coordinator
Managed Care
Chief Financial Officer
Financial Counseling



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